IL36RN Mutations Underlie Impetigo Herpetiformis

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TO THE EDITOR

Impetigo herpetiformis (IH) is a rare pustular dermatosis that typically occurs in pregnant women sporadically with unknown etiology (Sauer and Geha, 1961). Early diagnosis is essential, as IH is life-threatening and is associated with placental insufficiency and electrolyte abnormalities. IH appears to have the same clinical and histologic appearance as generalized pustular psoriasis (GPP), which is also a rare severe episodic pustular dermatosis that occurs repeatedly in both sexes at any age. However, some researchers have regarded IH as an entity distinct from GPP, because some patients are affected by IH only in the gestational period (Lotem *et al.*, 1989). Recently, we reported that the majority of GPP that is not accompanied by psoriasis vulgaris (PV; GPP alone) is caused by homozygous or compound heterozygous mutations of *IL36RN*, which encodes IL-36 receptor antagonist (IL-36RN), although only a small number of cases with GPP preceding or accompanied by PV (GPP with PV) were found to have *IL36RN* mutations (Sugiura *et al.*, 2013). Very recently, we reported that *CARD14* c.526G>C is a significant risk factor for GPP with PV, but not for GPP alone in the Japanese cohort, which further supports the idea that GPP with PV differs genetically from GPP alone (Sugiura *et al.*, 2014a). However, to our knowledge, there have been no reports of IH with *IL36RN* mutations. Here we report two cases of IH with homozygous and heterozygous *IL36RN* mutations.

Cases 1 and 2 were a 23-year-old woman and a 28-year-old Japanese woman who were admitted to our hospitals for pustular lesions in the 29th week and the 20th week of their first pregnancies, respectively (Figure 1a and b). There was no family history of GPP, no IH, and no consanguinity in their families. Case 1 had no previous history of GPP. Her pustular lesions had begun to develop at the 21st week of pregnancy, and she had been hospitalized in a maternity hospital. Oral prednisolone at a dose of 15 mg per day had been administered, but the eruptions had persisted. A skin biopsy from a pustular eruption on the trunk revealed a spongiform pustule of Kogoj in the epidermis consistent with IH (Figure 1c). Case 2 had suffered from GPP from the age of 8 to 18 years. Skin biopsies from pustular eruptions on the trunk revealed spongiform pustules of Kogoj in the epidermis at the age of 8 and 28 years (Figure 1d). She had been admitted to hospitals four times for GPP flare-ups. She had been treated with cyclosporine or etretinate. In the ten years leading up to her pregnancy, her GPP had been in remission without any treatment. Both cases had erythema with pustules over the whole body and fever of over 38 °C. Blood examinations from Cases 1 and 2, respectively, revealed white blood cell counts of 12,000 μl^{-1} and 21,170 μl^{-1}, and C-reactive protein concentrations of 6.5 and 14.9 mg dl^{-1} (normal range: <0.3 mg dl^{-1}). Bacterial cultures of the pustules were negative. Thus, Cases 1 and 2 were, respectively, diagnosed as having IH and IH with a previous history of GPP.

Following ethical approval, written informed consent was obtained in compliance with the Declaration of Helsinki Principles. The entire coding regions of *IL36RN* including the exon/intron boundaries were sequenced using genomic DNA samples from the patients. Case 1 had the homozygous mutation c.115+6T>C, which was proven to result in p.Arg10ArgfsX1 in *IL36RN* by us previously, and Case 2 had the heterozygous mutation c.28C>T (p.Arg10X) in *IL36RN*. Both of these are GPP-causing founder mutations in the Japanese cohort (Sugiura *et al.*, 2013, 2014b; Figure 1e and f, and Figure 2). A search for a second *IL36RN* mutation in all intron and putative promoter regions in Case 2 revealed no other *IL36RN* mutations (Supplementary Figure S1 online and Supplementary Table S1 online). However, there is still the possibility of a second unidentified *IL36RN* mutation in Case 2.

More than 10 cases of GPP with heterozygous *IL36RN* mutations have been reported (Capon, 2013; Korber *et al.*, 2013; Li *et al.*, 2013; Setta-Kaffetzi *et al.*, 2013; Sugiura *et al.*, 2013). Moreover, in some patients, heterozygous *IL36RN* mutations are associated with palmoplantar pustulosis, a type of pustular psoriasis, and acute generalized exanthematous pustulosis, a severe cutaneous drug reaction (Navarini *et al.*, 2013; Setta-Kaffetzi *et al.*, 2013). IL-36 is absent in normal skin but is induced by inflammatory cytokines such as tumor necrosis factor-α, IL-17A, and IL-22 (Carrier *et al.*, 2011). When functional IL-36RN is absent or underproduced, overexpressed IL-36 can induce neutrophil-rich infiltration. Tumor necrosis factor-α is often elevated in the blood of pregnant women, whereby it induces various serious diseases (Mallmann *et al.*, 1991). As for skin diseases, tumor necrosis factor-α sometimes causes exacerbation of PV lesions in pregnant women (Puig *et al.*, 2010). Hence, it is very likely that a pregnant woman who has the *IL36RN* mutation occasionally cannot produce enough IL-36RN to adequately antagonize IL-36 excessively induced by inflammatory cytokines, and this imbalance results in IH.

After longstanding controversy over whether IH is an independent disease

Abbreviations: GPP, generalized pustular psoriasis; IH, impetigo herpetiformis; IL-36RN, IL-36 receptor antagonist; PV, psoriasis vulgaris

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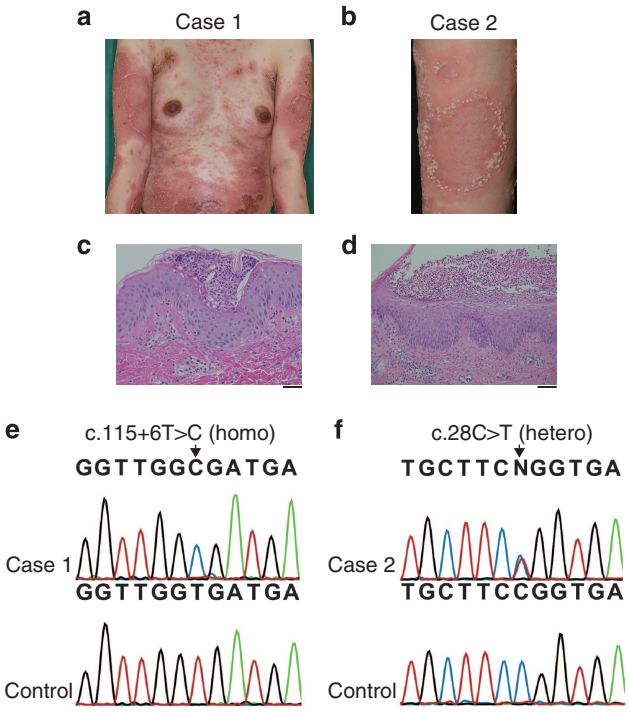

Figure 1. Clinical features, pathological findings of pustules, and mutation analysis of *IL36RN* in the patients. The clinical features of Cases 1 and 2 (**a**, **b**) are shown. Pustules on background erythema are seen on the trunk and arms. The pathology of the pustules is indicated for Cases 1 and 2 (**c**, **d**). Spongiosis of Kogoj and acanthosis are observed in the epidermis of the pustular erythematous lesions on the trunks. Scale bar = 50 μm for **c** and 100 μm for **d**. Direct sequencing reveals the homozygous mutation c.115 + 6 T>C in Case 1 (**e**) and the heterozygous mutation c.28C>T in Case 2 (**f**).

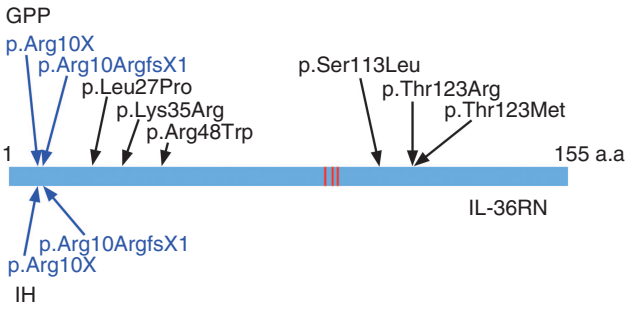

Figure 2. The second structure of IL-36RN and location of all *IL36RN* mutations ever reported in generalized pustular psoriasis (GPP) and impetigo herpetiformis (IH). All *IL36RN* mutations ever reported in GPP and IH (including in the present report) are shown (Kanazawa *et al.*, 2013). The blue characters indicate truncating mutations, and the black characters indicate missense mutations. Red lines show critical residues that mediate receptor interaction, such as Tyr89, Glu94, and Lys96 of IL36-RN (Sugiura *et al.*, 2013).

entity from GPP, today there is the consensus that IH is not a distinct entity but is identical to GPP, i.e., IH is GPP occurring during pregnancy (Lotem *et al.*, 1989; Robinson *et al.*, 2012). However, there have been no reports with experimental or genetic evidence to bolster the assertion that IH and GPP are identical diseases. This report clearly shows IH patients with homozygous or heterozygous *IL36RN* mutations. Case 1 was affected with IH only once in the gestational period. In this context, the present case suggests that IH and GPP, especially GPP alone, are identical diseases caused by *IL36RN* mutations. Future study should elucidate the proportion of IH cases that are *IL36RN* negative; however, given that the majority of GPP alone is associated with *IL36RN* mutations, we consider that mutation analysis of *IL36RN* is a very promising method for the prediction of IH risk to prevent subsequent serious complications in the patient and the fetus.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Kazumitsu Sugiura[1], Naoki Oiso[2], Shin Iinuma[3], Hiromasa Matsuda[2], Masako Minami-Hori[3], Akemi Ishida-Yamamoto[3], Akira Kawada[2], Hajime Iizuka[3] and Masashi Akiyama[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Faculty of Medicine, Department of Dermatology, Kinki University, Osaka-Sayama, Japan and [3]Department of Dermatology, Asahikawa Medical University, Asahikawa, Japan
E-mail: kazusugi@med.nagoya-u.ac.jp or makiyama@med.nagoya-u.ac.jp

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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